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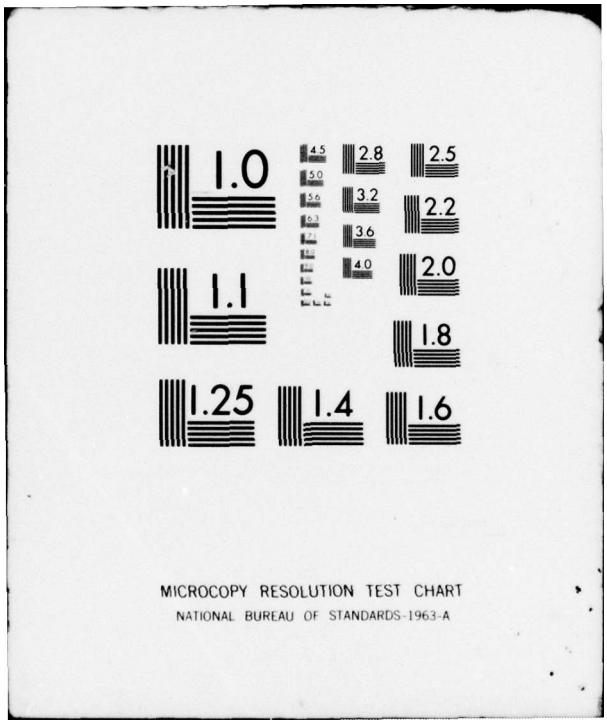
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FINAL REPORT

(Themis Project)

OFFICE OF NAVAL RESEARCH

Contract N00014-69-A-0426
Task No. NR 108-876

Bioamines in Stress

by

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Hahnemann Medical College and Hospital

December 1, 1976

This research was supported in part by the Office of Naval Research, Biochemistry Program, Naval Biology Project, under Contract No. N00014-69-A-0426, NR 108-876.

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER: 4
2. GOVT ACCESSION NO.
3. RECIPIENT'S CATALOG NUMBER

4. TITLE (and Subtitle): Bioamines in Stress
5. TYPE OF REPORT & PERIOD COVERED: Final Rept. no. 4 1 Jul 69-30 Jun 74
6. PERFORMING ORG. REPORT NUMBER: 763-23-0100
7. AUTHOR(s): E. T. Angelakos M.D., Ph.D.
8. CONTRACT OR GRANT NUMBER(s): N00014-69-A-0426
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Dept. of Physiology & Biophysics, Hahnemann Medical College & Hospital, 230 N. Broad St., Phila., PA 19102
10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: NR 108-876
11. CONTROLLING OFFICE NAME AND ADDRESS: Office of Naval Research, Arlington, Virginia 22217
12. REPORT DATE: 1 December 1976
13. NUMBER OF PAGES: 18p.
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office): ONR Resident Representative, 209 South 33rd Street, Philadelphia, PA 19174
15. SECURITY CLASS. (of this report)
15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)
Approved for public release; distribution unlimited.
(9) Rept. no. 4 (Final) 1 Jul 69-30 Jun 74,

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)
Approved for public release; distribution unlimited.

18. SUPPLEMENTARY NOTES
Most of the results and conclusions were published in scientific papers or have been reported at scientific meetings between 1970-1976, (totaling more than 100 publications and reports).

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)
adrenergic system, central nervous system, bioamines, stress, dogs; pigs, subhuman primates, physiology of stress, biochemical responses to stress, bibliography on stress.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
The role of various forms of stress in activating the adrenergic nervous system and release of bioamines in the brain & periphery was studied in a number of experimental animal preparations in dogs, pigs & nonhuman primate. Extensive information was collected on several forms of stress, their biochemical responses & in connection with the role of the central adrenergic system & lipid metabolism. Most of the findings were published in scientific journals and/or reported in scientific meetings. A total of 110 publications (full-length papers, abstracts & other reports) which resulted from these studies, including several collaborative studies are listed with complete bibliographic information.

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Final Report

A. List of Participating Scientists

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H. E. Appert, Ph.D.	Assistant Professor
W. A. Black, M.D.	Resident
R. A. Bonner, D.V.M., Ph.D.	Assistant Professor
J. Carballo, M.A.	Senior Instructor
L. Carballo, M.A.	Senior Instructor
W. S. Chernick, D.Sc.	Professor
J. Chimoskey, M.D.	Associate Professor
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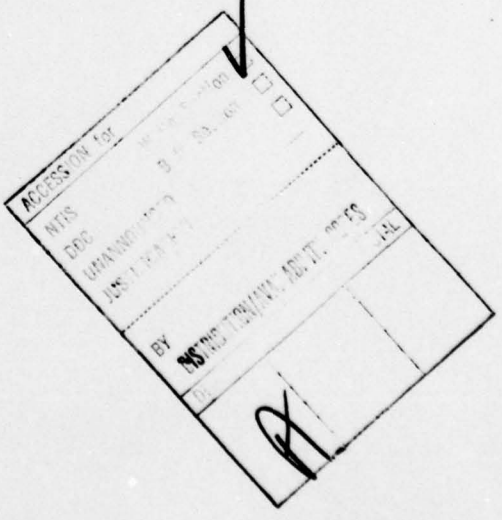
R. Goldfarb, B.S.	Graduate Student
C. Hollshwandner, Ph.D.	Assistant Professor
J. M. Howard, M.D.	Professor
J. Irvin, Ph.D.	Graduate student
K. Kalkhof, M.S.	Instructor
M. P. King, M.S.	Senior Instructor
A. G. B. Kovach, M.D.	Visting Professor
J. Little, M.D., Ph.D.	Research Assistant Professor
R. Millard, Ph.D.	Visiting Instructor
L.C. Mills, M.D.	Professor
J.L. Osterholm, M.D.	Professor
J.T. Ponessa, Ph.D.	Assistant Professor
E.A. Reed, Ph.D.	Associate Professor
R. Riley, Ph.D.	Graduate Student
S. Robinson, Ph.D.	Assistant Professor
J.C. Scott, Ph.D.	Professor
M.J.C. Showers, Ph.D.	Associate Professor
J.J. Spitzer, M.D.	Professor
J. Spitzer, Ph.D.	Research Associate Professor
A. Sternberg, Ph.D.	Assistant Professor
J.C. Torres, Ph.D.	Professor and Vice Chairman
R. Wiener, M.D.	Research Associate Professor



B. Objectives

The project is based on the premise that stress involves an activation of the adrenergic nervous system and the release of neurohumoral bioamines within and outside the CNS which may be responsible for a number of the biochemical and functional changes observed in stress. The overall objectives of this project are therefore to: a) evaluate the role of bioamines in biological stress; b) correlate bioamine release and turnover with cardiovascular and metabolic reactions to stress; c) study the biochemical basis of various reactions to stress; and d) identify biochemical indices for various forms of stress.

C. Summary of Work and Findings

During 1970-71, a number of specific studies were initiated and pursued dealing with various aspects of the overall project. These included: 1) catecholamine levels and histochemical studies of adrenergic fibers in specific regions of the cat and squirrel monkey brain; 2) role of the adrenergic innervation of the carotid sinus in cardiovascular responses; 3) adrenergic mechanisms in the cardiovascular effects of controlled acute cerebral trauma and the role of central amines; 4) hepatic and myocardial fatty acid metabolism following severe hemorrhage; 5) intestinal blood flow and oxygen consumption in the conscious dog; 6) sympathetic control of intestinal motility; 7) intestinal absorption in stress including endotoxin shock (dog); 8) adrenergic responses in the salivary gland; 9) carotid sinus responses in hyperthermic animals; 10) urinary catecholamines in man in exercise-in-heat stress (in collaboration with U.S. Army laboratories for Environmental Medicine, Natick, Mass.); 11) Renal blood flow in acceleration stress in the conscious dog (conducted at the U.S. Naval Air Development Center, Johnsville, Pa.).

Some of the significant findings included: 1) An extensive adrenergic innervation of the blood vessels of the hypothalamus in all the laboratory species examined which may account for as much as 25-30% of norepinephrine found in this region and may play a critical role in the reactions of the hypothalamic control centers to stress. 2) Adrenergic innervation in the carotid sinus regions which alters the baroreceptor responses to blood pressure changes and thus may provide different "settings" for this key cardiovascular reflex in stress. 3) Cerebral trauma is associated with a centrally mediated withdrawal of adrenergic support to the heart and blood vessels which accounts for the bradycardia and shock levels of hypotension. Hypothalamic serotonin may be involved as the central inhibitor in this condition. 4) Following severe hemorrhage in the dog, the arterial free fatty acid (FFA), total body FFA flux and hepatic uptake and oxidation of FFA and triglyceride output all decreased while hepatic ketrogenesis increased. The non-hepatic splanchnic area oxidized less FFA and removed ketones. Myocardial FFA oxidation was also reduced and other metabolites contributed more to the myocardial metabolism following hemorrhage. 5) A method was developed for measuring intestinal blood flow and oxygen consumption in

a segment of the intestine in the conscious dog. 6) Certain forms of stress produce inhibition of intestinal motility which appears to be due to adrenergic inhibition of intestinal smooth muscle. 7) Endotoxin shock in the dog is associated with a net transport of water and electrolytes in the intestinal lumen. 8) A colony of immunosympathectomized rats was developed to study adrenergic control of salivary secretion. 9) Moderate hyperthermia reduces the heart rate effects following increase in intra-carotid pressure. 10) No significant differences in urinary catecholamines were found in man exercising in heat in the supine vs. erect position. 11) Negative acceleration in the unanesthetized dog is associated with vasoconstriction in the renal vascular bed.

Major emphasis in the studies conducted in 1971-73 was placed into two general areas: a) central nervous system mechanisms in hemorrhagic shock; and b) gastrointestinal function in hemorrhagic and endotoxic shock. The role of bioamines was examined in each case. Specific emphasis was placed on the blood vessel control by adrenergic fibers in the brain and gastro-intestinal tract. In addition, a number of collaborative studies were conducted.

The specific studies which were continued or new studies begun during 1971-73 dealing with the various aspects of the overall project included: 1) Determination of regional blood flow in the brain during sympathetic stimulation and the effect of adrenergic blocking agents; 2) Hypothalamic blood flow in hemorrhagic shock; 3) Modification of the responses to hemorrhagic shock by administration of adrenergic blocking agents in the cerebral circulation; 4) Quantitation of intraneuronal concentration of amines in microscopic regions of the brain as a means of evaluating effects of stress on specific neurons and tracts; 5) Comparative studies in canine and primates on gastrointestinal water and electrolyte absorption in endotoxin shock; 6) Effects of acute severe hemorrhage on intestinal metabolism; 7) Computer evaluation on the effects of bioamines on the ECG, extension into human ECG during exercise; 8) Plasma catecholamine responses in man exercising at high altitudes (in collaboration with scientists of the U.S. Army Institute for Environmental Medicine in their recent studies at Pikes Peak, Colorado); 9) Isolation of adrenergic synaptosomes from brain homogenates to determine possible correlation with certain prostaglandins found in brain (in collaboration with Dr. Polis of the U.S. Naval Air Development Center); 10) Evaluation of amine binding by platelets during hemorrhage and influence of platelet aggregation (in collaboration with Dr. H. Berman of Boston University); 11) Continuation of studies on the role of the adrenergic system and locally released catecholamines in spinal cord injury (in collaboration with Dr. J. Osterholm of the division of Neurosurgery); 12) Evaluation of plasma and urinary catecholamine levels in patients under various forms of stress (in collaboration with Dr. G. Onesti).

Some of the significant findings include: 1) Blood vessels in hypothalamus, thalamus and most regions of the brain stem are under sympathetic adrenergic control and apparently participate in the general vasoconstriction observed in hemorrhagic shock. 2) Evaluation of intraneuronal concentration of bioamines

in specific neurons and tracts of the brain is now possible using histochemical techniques and microspectrofluorometry. 3) Analyses of an entire region of the brain (e.g. hypothalamus) using conventional biochemical techniques do not necessarily reflect the changes occurring in specific functional parts of that region. 4) Water and electrolyte transport across the gastrointestinal tract play a significant role in the functional and metabolic alterations observed in endotoxin shock. In this respect, there are marked differences between canine and the primate species. 5) Intestinal metabolism as evaluated by oxygen consumption and substrate utilization is greatly altered during hemorrhagic shock. 6) The catecholamine response to exercise in man is greater at high altitude than at sea levels and there is no apparent adaptation in this over a week's period. Plasma catecholamines appear to be a good biochemical index of stress in this case. 7) A large fraction of the morbidity and functional impairment observed following acute spinal cord injury is associated with local release of adrenergic amines at and proximal to the region of injury. Pharmacological modification of this adrenergic response appears to be apromising therapeutic approach in this form of injury and may be applicable in injury of other parts of the central nervous system.

Some of the major conclusions reached include: 1) Changes in the gastrointestinal tract especially in connection with transport of water and electrolytes across this tract deserve further study in attempts to elucidate the mechanism of circulatory shock. However, species differences are of particular significance in this case. These differences may be due to differences in adrenergic control of splanchnic blood vessels (e.g. canine vs. primate). 2) Blood flow within certain regions of the central nervous system is apparently under adrenergic nervous control. This heretofore unrecognized mechanism could play a key role in states of general adrenergic discharge as it occurs in many forms of severe stress, e.g. hemorrhage, major local injury, etc. This could be directly responsible for some irreversible effects observed in such forms of stress (e.g. irreversible hemorrhagic shock). Modification of the biochemical mechanisms involved in the production, release and action of the adrenergic amines associated with the innervation of the blood vessels in the central nervous system could provide a new approach to the treatment of some of these conditions. New pharmacological agents which act specifically in these regions should be sought and developed.

During the last phase, 1974-75, of this project, major emphasis was placed in completing studies begun previously relating to stress associated with cardiovascular insults (hemorrhagic shock, cardiogenic shock) and the role of peripheral and central mechanisms involving bioamines in these states.

Over this period, major emphasis was placed in two general areas: a) continuation of studies on central nervous system mechanisms in hemorrhagic shock and b) evaluation of hemorrhagic shock in the pigs as a potentially better model for hemorrhagic shock in man. In addition, a few other collaborative studies were conducted.

The specific studies made during this period include: 1) influence of cervical sympathetic innervation of cerebral vessels on regional brain blood flow; 2) development of a model for irreversible hemorrhagic shock in the domestic pig; and 3) evaluation of magnetocardiography as a non-inversive index of cardiac status (including preliminary studies in the effect of hemorrhage).

In addition, a number of previous studies were completed (see publications). Furthermore, two collaborative studies were conducted, one with Dr. J. Maher of the U.S. Army Laboratories for Environmental Medicine on the effect of high altitude (U.S. Army Study in Peru) and exercise at high altitude on plasma catecholamine levels in man and one with Dr. Polis of the Naval Air Development Center, Warminster, Pa. on the effect of PGBx in shock. Although these latter studies were funded separately, they did use facilities and expertise developed as a result of this "Themis" project. Finally, work originally begun with this project and conducted by Dr. John Spitzer, Dr. Judy Spitzer, Dr. Robert Alteveer and Dr. Anne Ambromovage is now under four other separate contracts and so reported. The results of the studies funded during the terminal year of this contract can be summarized as follows:

I. Studies on cerebral vessel responses were first made in cats with stereotaxically placed sensors using the thermal washout technique. It was found that cervical sympathetic stimulation reduced significantly (approx. 30%) cerebral blood flow. In these animals the probes were in the ventricle thalamus near the midline. Histofluorescence examination of this region demonstrated the presence of small blood vessels with distinct adrenergic innervation. Pretreatment with alpha adrenergic blocking drugs abolished these flow reduction responses to cervical sympathetic stimulation. In another series of experiments (12 cats) the role of this mechanism was examined in moderate to severe hemorrhagic shock. In these animals cervical sympathectomy produced after 30 min. to 1 hour of shock, produced no significant alterations in regional blood flow. To test the possibility that the reflex adreno-medullary response might be involved and thus mask any effect of local sympathetic innervation another series of studies was made, in this case in the dog with bilateral adrenalectomy. In these animals, 30 min. to 1 hour in shock, cervical sympathectomy produced a significant increase in blood flow in certain regions of the brain. However, it has not been technically possible as yet to place flow probes in the critical areas of the hypothalamus where most of the blood vessel adrenergic innervation has been demonstrated with the histofluorescence technique. Furthermore, the role of this system in the irreversible form of shock would be of particular significance as would be information on the role of this innervation on the autoregulation of brain blood flow in response to changes in blood pressure. Studies are now in progress to examine these relationships.

2. A number of different approaches were used in the development of an experimental model for irreversible hemorrhagic shock using the domestic pig as the experimental animal. Previous studies in this and other laboratories have indicated many similarities in the cardiovascular and biochemical responses to hemorrhagic shock in pigs and man. Initial attempts to develop a reproducible response to hemorrhagic shock in pigs gave extremely variable responses.

For instance in a series of experiments, slow blood loss (over a 1 hour period) indicated that reduction of blood volume up to 40% of total did not produce irreversible shock in any of the animals. However, further reduction to 45% produced a very high percentage of precipitous deaths. More rapid bleeding reduced the level of lethal blood loss (to 40%), but the responses to reinfusion were extremely variable. In general, these in vitro studies indicated that there was a critical level of blood loss that led to progressive cardiovascular deterioration and death, but his level was quite different in different animals. This is very like the situation described for acute hemorrhage in normal healthy men (in contrast to conditions found after a debilitating disease) and further emphasizes the similarities in the responses between man and pig.

A protocol which results in a consistent development of irreversible shock was eventually developed. This involves rapid blood removal leading to a mean blood pressure of 50 mmHg. which is maintained (by further blood removal) for a period of 60 minutes. In these animals, the blood loss amounts to 35-40% of their blood volume. Re-infusion of blood at the end of the 60 minute period provides no lasting cardiovascular recovery and leads to death from irreversible shock over the next 20 to 60 minutes. The cardiovascular parameters monitored in these animals included: ECG, heart rate, systolic & diastolic pressures, left ventricular pressure (LVP, rate of rise of LVP (dP/dt), end-diastolic pressure, etc. Plans are also in progress to determine continuous cardiac output (by aortic flow probe), and blood gases. Plasma and tissue catecholamine levels will be also measured. In addition, some preliminary measurements have been made on the status of the circulating platelets (including their amine content) which may play a significant role in shock and/or be altered by the biochemical responses to shock. Plans have also been made to measure plasma prostaglandin levels. In general, it is concluded that the pig provides a good experimental model for hemorrhagic shock as observed in young healthy men.

D. Conclusions:

The role of bioamines and other biochemical indices of stress was examined in specific studies conducted in a variety of experimental conditions in a wide range of animal species (mostly in dogs, pigs, nonhuman primates) with a few limited studies in man. These studies provided extensive basic information on specific biochemical aspects of different forms of stress which can be utilized in evaluating the degree of stress, the metabolic responses to stress and ultimately, the functional (physiological and biophysical) consequence of stress. The specific information collected was published in the open literature in appropriate scientific journals and/or was reported in scientific meetings, symposia, etc. A total of 110 publications and/or reports results from these studies between 1969 to 1976 (see attached list). Additional information appeared in subsequent publications made by the investigators involved when these studies were extended at Hahnemann as well as in other institutions.

The primary aim of the Themis project was met by: a) the development of strong capabilities within this laboratory and this Institution for work relating to stress and its biochemical consequences; and b) the accummulation of basic information relating to the functional alterations during stress including potential approaches for limiting its detrimental effects.

As a result of the Themis project, several subsequent studies were conducted under new contracts with some of the participating investigators (Drs. Angelakos, Alteveer, Ambromovage and Spitzer) at Hahnemann and later at Louisiana State University (where Dr. Sptizer's group moved). Work is still continuing at Hahnemann under contract with ONR on projects based on information initially developed during the Themis project. In addition, several investigators involved in the Themis project applied and received support from the NIH and other agencies for the extension of work the basis of which was developed during the Themis project.

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*Indicates collaborative studies.